

Appl. No. 10/056,749
Amdt. dated October 21, 2005
Reply to Office Action of April 21, 2005

PATENT

Amendments to the Drawings:

Please replace Figures 8, 11, and 13 with the replacement formal drawings provided in Appendix A. The only changes relate to formalities. Accordingly, no annotated pages are provided.

Attachment: Replacement Sheets for Figures 8, 11, and 13

REMARKS

With entry of the instant amendment, claims 29, 44, 46, and 47 have been amended and claims 35-43 and 48 have been cancelled. Claims 1-28 were previously cancelled; accordingly, claims 29-34 and 44-47 are under examination.

Claims 35-43 and 48 are cancelled without prejudice to subsequent revival for prosecution in a divisional application.

The amendments to claims 29, 44, 46, and 47 add no new matter and are fully supported in the specification. Claims 29 and 44 have been amended to recite a comparison to a gene expression profile from a long term calorie-restricted mammal and identifying changes that correlate with changes occurring in long term caloric-restricted mammals. Support can be found, *e.g.*, on page 14, lines 5-12. Claims 46 and 47 have been amended to further clarify the claims as explained below.

The amendments to the specification add no new matter. The amendments were made in light of the submission of black and white figures for Figures 8, 11, and 13; and to correct formalities relating to the use of a registered trademark and a URL.

Priority claim

The Examiner has only granted priority to the parent application 09/648,642, filed August 25, 2000. The '642 application is a continuation-in-part of application 09/471,224, filed December 23, 1999. The Examiner did not grant priority to the '224 application because the Application Data Sheet, the Oath/Declaration, and the first line of the specification do not claim priority to the '224 application. However, on December 13, 2002, Applicants filed a Petition for the Benefit of a Prior-Filed Co-pending Nonprovisional Application including the petition fee; a statement that the entire delay between the date the claim was due and the date of filing the claim was unintentional; a Request for a Corrected Filing Receipt; an updated Application Data Sheet and a copy of the Supplemental Application Data Sheet dated May 16, 2002 showing the changes; and a copy of a Certificate of Correction in the priority application number that was filed in the parent '642 application, now U.S. Patent No. 6,406,853. This petition was granted

(see, Paper No. 10, mailed April 2, 2003). Accordingly, Applicants have corrected the priority claim. Applicants therefore respectfully request that the priority reflect the claim to the '224 application.

Drawings

The Examiner required replacement drawing for Figures 8, 11, and 13. The amendment to the drawings provide replacement sheets in which the contents of the drawings can be viewed.

Applicants have also amended the specification at page 4 and pages 8-10 as shown in the **Amendments to the Specification** in view of the submission of black and white drawings in this application.

Rejections under 35 U.S.C. § 112-second paragraph

Claims 29-34 and 44-47 were rejected as allegedly indefinite. The Examiner contends that the claims do not clarify the relationship between identifying changes in a gene expression profile and obtaining a biomarker. With regard to claims 46 and 47, the Examiner alleges that it is unclear as to how the identification of changes that occur in both the young and old calorie-restricted animals or in only the young or old calorie restricted animals is used to obtain the biomarker of calorie restriction. Although Applicants believe that the claims as filed were clear, in order to expedite prosecution, the claims have been amended to further clarify the nexus between the preamble and process steps. Applicants therefore respectfully request withdrawal of the rejections.

Rejection under 35 U.S.C. § 102(e)

Claims 29, 33, 34, and 44-47 stand rejected as allegedly anticipated by Weindruch *et al.* in U.S. Patent No. 6,569,624 (referred to herein as "Weindruch"). The Examiner alleges that Weindruch discloses a method comprising determining the gene expression profile of a young mammal (a mammal at five months), a mature mammal (a mammal at 30 months), a

calorie-restricted mammal at five months, and a calorie restricted mammal at 30 months; and comparing the gene expression profiles in order to identify changes in gene expression profiles. In particular, the Examiner cites to columns 7, 8, and 10 and the comparisons of five-month-old animals to 30-month-old control and caloric restricted mice in Tables 1-10. In so far as the rejection replies to the amended claims, Applicants respectfully traverse.

First, Applicants corrected priority predates the earliest priority document for Weindruch. Accordingly, Weindruch is not prior art.

Second, even assuming *arguendo* that Weindruch could be viewed as prior art, Weindruch does not disclose that the calorie-restricted animals are on the calorie-restricted diet for a period of time that is less than lifelong, in the sense that the terms "lifelong" and "long term calorie restriction" are used in the instant application. The specification makes clear that lifelong and long term calorie restriction are used interchangeably to refer to calorie restriction that is imposed for most of the animals life. For example, on page 1, lines 19-21 teaches that it is well known that long term reduction in dietary calorie consumption delays most age-related physiological changes. The examples also teach long term calorie restriction in which the animal spends most of its life on a calorie restricted diet (*see, e.g.*, example 1 beginning on page 16 and page 25, lines 1-2). Such long-term treatment is also referred to as lifelong calorie restriction (*see, e.g.*, page 55, lines 28-30). Further, Lee *et al.* (a copy of which was provided with the IDS filed July 21, 2001 in the parent application and for convenience, is provided in Appendix B attached hereto) is cited on page 1, line 30 bridging to page 2, line 4 as teaching one study of long term calorie restriction. The long term calorie restricted animals in Lee *et al* spend the majority of their lifetime on a calorie restricted diet (*see*, page 1391, third column, first sentence of the first full paragraph). Thus, long-term or lifelong calorie restriction refers to a regimen in which animals spend most of their lives on a calorie restricted diet. In the instant application, mammals are subjected to short-term calorie restriction in which treatment is less than lifelong and the animal spends more time on a normal diet than a calorie restricted diet.

Additionally, Weindruch describes changes in gene expression in young versus mature mice (so-called "aging related" changes in gene expression), but does not disclose calorie

restriction of young animals, only mature animals. Column 7, lines 36-41 describes that calorie restriction was in 30-month old animals. Tables 3, 4, 7, 8, for example, show changes in gene expression in only one set of calorie-restricted animals, that observed in long term calorie restriction of mature animals. Thus Weindruch also fails to teach this element of the claimed invention.

In view of the foregoing, Weindruch does not anticipate claims 29, 33, 34, and 44-47. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 29, 33, 34, and 44-47 stand rejected as allegedly anticipated by Mote *et al.*, *J. Gerontol.* 46:B95-100, 1991 (referred to herein as "Mote"). The Examiner contends that Mote discloses a method comprising determining the gene expression profiles of each of a mammal young mammal (a mouse at 4-5 months), a "middle-aged" mammal (a mouse at 16-17 months), and a mature or old mammal (a mouse at 30-31) months, and gene expression profiles of calorie-restricted animals matched for the ages. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

The calorie-restricted animals describe by Mote were not subjected to a period of calorie restriction that was less than life-long, as the term is understood in the instant specification, *supra*. Furthermore, Mote does not disclose that changes in gene expression profiles were observed with calorie-restriction in young animals in comparison to animals of the same age. The changes in mRNA levels of P1-450, P3-450, SOD, and catalase in young animals subject to different dietary regimens were not statistically significant (*see, e.g.*, the legends of Figure 1, 2, 3, and 4, which indicate that bars with the same letter are not significantly different). In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 103-Weindruch in view of Chu and Tillman

Claims 30-32 were rejected as allegedly unpatentable over Weindruch in view of Tillman *et al.*, *J. Biol. Chem* 271:2500-2506, 1996 (referred to herein as "Tillman") and Chu, *et*

al. Mechanisms of Ageing and Development 87:25-33, 1996 (referred to herein as "Chu"). The Examiner alleges that Weindruch teaches that the period of caloric restriction extended from approximately 1 month to 4/5 months, 16/17 months and 30/31 months. Weindruch does not teach caloric restriction of 6 weeks, 2 weeks, or 2 day or less. The Examiner contends that Chu and Tillman teach that long term caloric restriction is known to reverse or delay age-related physiological changes and, as both references teach that short-term CR effects gene expression, it would have been obvious to modify the invention of Weindruch to administer a caloric restricted diet for a short period of time. Applicants respectfully traverse this rejection.

As the Examiner knows, in order to establish a proper *prima facie* case of obviousness, the Examiner must establish that there is a suggestion or motivation to modify the references or to combine the reference teachings; there must be a reasonable expectation of success; and the references or combination of references must teach or suggest all of the claim limitations (*see, e.g.*, MPEP § 2142). The teachings or suggestions to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cr. 1991)). The arguments advanced by the Examiner fail to meet these criteria.

Applicant's invention is based on the discovery that gene expression profiles induced by short-term caloric restriction mimic those induced by long-term caloric restriction (*see, e.g.*, page 14, lines 5-7). Accordingly, the claimed invention is drawn to identifying biomarkers by calorie-restricting animals for short periods of time. Markers induced by short term calorie restriction that reflect the beneficial changes in gene expression profiles obtained by long-term calorie restriction can therefore be used as biomarkers, *e.g.*, for screening for interventions that mimic calorie restriction.

Applicants acknowledge that changes in diet influence gene expression patterns. However, prior to Applicant's invention, one of skill in the art could not have reasonably expected to be able to use short-term calorie restriction as a method for obtaining biomarkers that are useful for identifying interventions that provide the beneficial effects of long-term calorie restriction. For example, Chu teaches that short term calorie restriction augments the effects of

aging. Thus, one of skill would not be led to reasonably expect that short-term calorie restriction is an effective treatment regimen for obtaining biomarkers. Indeed, there is no evidence that one of skill would even have been motivated to examine global gene expression profiles in response to short-term calorie restriction for their ability to mimic effects achieved with long-term calorie restriction.

Tillman also provides no additional teachings that would lead one to Applicant's invention. Tillman merely teaches that changing the diet of a long-term calorie-restricted mouse to an ad libitum diet changes levels of cpsI mRNA after a week. The Examiner has provided no evidence or reasoning that would lead one to expect that decreasing calories for a short time-period would achieve the opposite effect and mimic the effects of long-term calorie restriction. In fact, prior art references such as Chu would be more likely to lead one of skill to expect the opposite. Thus, the suggestion that the ordinary artisan would have been motivated to perform short term calorie restriction at best, amounts to an invitation to experimentation. In view of the foregoing, the Examiner has not established a proper case of *prima facie* obviousness. Applicants therefore respectfully request withdrawal of the invention.

Rejections under 35 U.S.C. § 103-Mote in view of Chu and Tillman

Claims 30-32 were also rejected as allegedly unpatentable over Mote in view of Tillman and Chu. The Examiner contends that both Chu and Tillman teach that long term calorie restriction is known to reverse or delay age-related physiological changes, and further that short-term calorie restriction effects gene expression. The Examiner argues that based on the teachings of Chu and Tillman, one of skill would have modified the method of Mote to have administered the calorie restricted diet for shorter periods of time to have studied the effects of short-term calorie restriction on gene expression. Applicants respectfully traverse this rejection for reasons explained above. In brief, although it is possible that one in the art would have been motivated to try short term caloric restriction, there was not reasonable expectation of success. In view of the foregoing, Applicant respectfully requests withdrawal of the invention.

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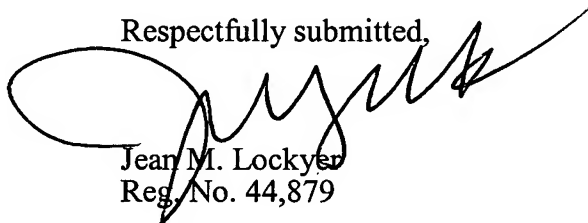
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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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